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Case 7670

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of	:	
D.N. Rubingh et al.	:	
Serial No. 09/618,235	:	#21
Confirmation No. 8554	:	Group Art Unit 1652
Filed July 18, 2000	:	Examiner W.W. Moore

For PROTEASE CONJUGATES HAVING STERICALLY PROTECTED EPITOPE REGIONS

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Examiner:

This Appeal Brief is submitted in support of the Notice of Appeal transmitted to the PTO via facsimile on February 6, 2003, which set a two-month period for response. A petition to extend the period for response four months from April 6, 2003 is submitted herewith in order that this Appeal Brief is deemed timely in its submission.

REAL PARTY IN INTEREST

The real party in interest is The Procter & Gamble Company of Cincinnati, Ohio. The Inventors, Donn Nelton Rubingh, David John Weisgerber, and Paul Elliott Correa, assigned their interest to the Procter & Gamble Company on July 13, 2000, June 16, 2000, and July 17, 2000 respectively. This assignment was recorded in the USPTO on August 1, 2003 at reel 13843 and frame 011.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the Appellants, Appellants' legal representative, or Assignee that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

On February 6, 2003, Appellants appealed the final rejection of pending Claims 1-6, 8, 9, 20, 21, and objection to claims 7 and 10-19 to the Board of Patent Appeals and Interferences ("the

Board"). Claims 1-21 were originally filed, and the claims were restricted to the extent that they describe a protease variant modified by substitution and conjugation at a position that corresponds to any one of positions 17, 52, 89, 134, 155, and 265 of the mature subtilisin BPN'. This Appeal Brief addresses Claims 1-21, in regard to the aforementioned restriction. A complete copy of the appealed claims is set forth in the Appendix.

STATUS OF AMENDMENTS

Claim 1 was amended after the final rejection. The amendment was entered by the Examiner, as indicated in the Advisory Action filed January 31, 2003.

SUMMARY OF THE INVENTION

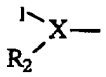
Claims 1-21 of the present invention relate to protease conjugates comprising a protease moiety and one or more addition moieties, wherein each addition moiety is covalently attached to an epitope protection position of the protease moiety, wherein:

(a) the epitope protection positions for the first epitope region are selected from 1, 2, 3, 4, 5, 6, 7, 12, 17, 36, 40, 41, 43, 44, 45, 67, 86, 87, 89, 206, 209, 210, 212, 213, 214, 215, and 216 corresponding to subtilisin BPN';

(b) the epitope protection positions for the second epitope region are selected from 25, 26, 27, 46, 47, 48, 49, 50, 51, 52, 53, 54, 91, 99, 100, 101, 102, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 140, 141, 144, and 145 corresponding to subtilisin BPN'; and

(c) the epitope protection positions for the third epitope region are selected from 9, 10, 22, 23, 24, 62, 63, 143, 146, 154, 155, 156, 157, 172, 173, 187, 189, 195, 197, 203, 204, 253, 254, 256, 265, 267, 269, 271, 272, and 275 corresponding to subtilisin BPN';

and wherein the addition moieties each, independently, have the structure:



wherein X is selected from nil and a linking moiety; R_1 is selected from nil, a first polypeptide, and a first polymer; and R_2 is selected from nil, a second polypeptide, and a second polymer; wherein at least one of X, R_1, and R_2 is not nil.

The protease conjugates of the present invention have decreased immunogenicity relative to the parent protease. Accordingly, such protease conjugates are suitable for use in several types of compositions including, but not limited to, laundry, dish, hard surface, skin care, hair care, beauty care, oral care, and contact lens compositions.

ISSUES

Appellants submit three issues for consideration by the Board:

(I) Whether Claims 5-18 are unpatentable under 35 U.S.C. §112, second paragraph as being indefinite?

(II) Whether Claims 1-6, 8, 9, and 20 are unpatentable under 35 U.S.C. §103(a) over US 6,300,116 (hereafter "Von der Osten") in view of US 5,766,897 (hereafter "Braxton")?

(III) Whether Claim 21 is unpatentable under 35 U.S.C. §103(a) over US 6,300,116 (hereafter "Von der Osten"), in view of US 5,766,897 (hereafter "Braxton"), in further view of US 6,060,546 (hereafter "Powell")?

GROUPING OF CLAIMS

Claims 1-21 stand or fall together.

ARGUMENTS

I. Claims 5-18, as amended on December 9, 2002, are definite.

The Advisory Action filed January 31, 2003 indicates that the amendment to Claim 1 filed by Appellants on December 9, 2002, overcomes the rejection.

II. Claims 1-6, 8, 9, and 20 are patentable over Von der Osten in view of Braxton because there is no motivation to combine the references.

Claims 1-6, 8, 9, and 20 have been finally rejected under 35 U.S.C. §103(a) as being unpatentable over Von der Osten in view of Braxton. Appellants respectfully submit that the compositions defined by claims 1-6, 8, 9, and 20 are nonobvious over and patentably distinguishable from Von der Osten in view of Braxton. As defined by Claim 1, the present invention is directed to protease conjugates comprising a protease moiety and one or more addition moieties, wherein each addition moiety is covalently attached to an epitope protection position of the protease moiety. The protease conjugates of the present invention have decreased immunogenicity relative to the parent protease, and are therefore useful in compositions such as laundry, dish, hard surface, skin care, hair care, beauty care, oral care, and contact lens compositions.

Appellants respectfully submit that the obviousness rejection should be withdrawn because the combination of Von de Osten and Braxton does not establish a *prima facie* case of obviousness because there is no motivation to combine the references. Therefore, Appellants contend that the claimed invention is unobvious and that Claims 1-6, 8, 9, and 20 should be allowed.

To establish *prima facie* obviousness of the claimed invention, there must be "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references". *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). There is no motivation to combine Von der Osten and Braxton, and therefore, the references do not establish a *prima facie* case of obviousness (see MPEP 2143.01).

There would be no motivation to combine Von der Osten's teaching of autoproteolytic stability with Braxton's teaching of immune surveillance. Autoproteolytic stability refers to a mechanism that hinders the protease from attacking itself. The immune surveillance technique, on the other hand, allows the protease to go unrecognized by a mammal's immune system. The issues of autoproteolytic stability and immune surveillance are completely separate problems. Thus, Von der Osten teaches protecting the protease from itself, and Braxton teaches protecting the protease from a foreign immune system. One skilled in the art would have no motivation to combine Von der Osten's teachings of altering amino acids for the purpose of increasing autoproteolytic stability with Braxton's teachings of masking a polypeptide from immune surveillance. Thus, the obviousness rejection does not establish a *prima facie* case of obviousness. Therefore, Appellants contend that the claimed invention is unobvious and that the rejection should be withdrawn.

The Examiner asserts that there is no need that the prior art supply the same motivation that Appellant had for making the product. However, Appellants contend that the prior art would not have provided one of ordinary skill in the art with *any motivation* to make the same product. Von der Osten teaches that making an amino acid substitution at a position corresponding to subtilisin BPN' position 134 will exhibit increased autoproteolytic stability. Thus, Von der Osten teaches targeting specific positions in order to keep the protease from attacking itself. Braxton teaches increasing protein stability in mammals by substituting amino acid residues with cysteine and attaching polyethylene glycol [PEG] to the cysteine, in order to mask epitopes that may be recognized by a mammalian immune defense system. Hence, Braxton teaches random cysteine substitutions at a polypeptide region followed by attaching PEG to the cysteine in order to protect it from immune surveillance.

While both Von der Osten and Braxton teach protection of the protein, the mechanisms in achieving the protection are clearly different and would not have motivated one of ordinary skill in the art to combine the references. One skilled in the art interested in the teachings of Von der Osten would be focused on protecting the protease from itself, as Von der Osten provided a method of

increasing autoproteolytic stability by substitutions at specific positions. Von der Osten does not teach or suggest that this method could be enhanced or applicable to any other form of protease protection. Further, Von der Osten never indicates that this method is insufficient to protect the protease from itself; therefore, one skilled in the art would have no motivation to search beyond the teachings of Von der Osten to find a better way to protect the protease from itself.

The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification, *In re Mills* 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Appellants find no such motivation in the teachings of Von der Osten and Braxton. Therefore, a *prima facie* case of obviousness has not been established, and Von der Osten and Braxton do not support a rejection under 35 U.S.C. §103. Since a *prima facie* case of obviousness has not been established, Appellants respectfully contend that this rejection should be withdrawn.

III. Claim 21 is patentable over Von der Osten in view of Braxton, in further view of Powell because there is no motivation to combine the references.

Claim 21 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Von der Osten, Braxton, and Powell. Appellants respectfully submit that the obviousness rejection should be withdrawn because the combination of Von der Osten, Braxton, and Powell does not establish a *prima facie* case of obviousness because there is no motivation to combine the references. Therefore, Appellants contend that the claimed invention is unobvious and that claim 21 should be allowed.

To establish *prima facie* obviousness of the claimed invention, there must be "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references". *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). There is no motivation to combine Von der Osten, Braxton, and Powell, and therefore, the references do not establish a *prima facie* case of obviousness (see MPEP 2143.01).

There is no motivation to combine Von der Osten, or Braxton with Powell. Powell only teaches the preparation of a personal care composition comprising subtilisin SP 544, while the other references specifically teach subtilisin modification and substitution. One skilled in the art would not be motivated to combine references teaching specific modifications or substitutions of specific regions of different subtilisins with Powell's general description of a personal care composition comprising subtilisin SP 544. Von der Osten specifically teaches altering amino acids in subtilisin 309 to inhibit proteolysis, and Braxton specifically teaches substitution of cysteine to then conjugate

polymers to protect from immune surveillance. While Powell teaches that subtilisins can be used in personal care compositions, there would be no motivation to combine that broad and general teaching with references teaching inhibition of proteolysis or polymer conjugation.

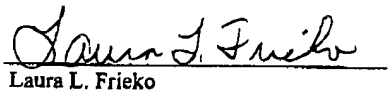
The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification, *In re Mills* 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Appellants find no such motivation in the teachings of Von der Osten, Braxton, and Powell. Therefore, a *prima facie* case of obviousness has not been established, and Von der Osten, Braxton, and Powell do not support a rejection under 35 U.S.C. §103. Since a *prima facie* case of obviousness has not been established, Appellants respectfully contend that this rejection should be withdrawn.

IV. SUMMARY

For the foregoing reasons, it is submitted that the rejection of Claims 1-21 under 35 U.S.C. §103 is erroneous. The Board's reversal of the rejections is respectfully requested.

Respectfully submitted,

Donn Nelton Rubingh, et al.

By 

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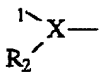
APPENDIX - APPEALED CLAIMS

1. A protease conjugate comprising a protease moiety and one or more addition moieties wherein the protease moiety comprises a first epitope region, a second epitope region, and a third epitope region, wherein each addition moiety is covalently attached to an epitope protection position of the protease moiety, wherein:
   (a) the epitope protection positions for the first epitope region are selected from the group of positions corresponding to positions consisting of 17 and 89 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1;
   (b) the epitope protection positions for the second epitope region are selected from the group of positions corresponding to positions consisting of 52 and 134 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1; and
   (c) the epitope protection positions for the third epitope region are selected from the group of positions corresponding to positions consisting of 155 and 265 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1.

2. A protease conjugate according to Claim 1 wherein each addition moiety, independently, has the structure:



   wherein X is selected from the group consisting of nil and a linking moiety; R_1 is selected from the group consisting of nil, a first polypeptide, and a first polymer; and R_2 is selected from the group consisting of nil, a second polypeptide, and a second polymer; wherein at least one of X, R_1, and R_2 is not nil.

3. A protease conjugate according to Claim 2 wherein the protease moiety has a modified amino acid sequence of a parent amino acid sequence, wherein the modified amino acid sequence comprises a substitution by a substituting amino acid at one or more of the epitope protection positions and wherein each addition moiety is covalently attached to one of the substituting amino acids.

4. A protease conjugate according to Claim 3 wherein the substituting amino acid is cysteine.

5. A protease conjugate according to Claim 4 wherein the parent amino acid sequence is selected from the group consisting of subtilisin BPN', subtilisin Carlsberg, subtilisin DY, subtilisin 309, proteinase K, thermitase, Protease A, Protease B, Protease C, and Protease D.

6. A protease conjugate according to Claim 5 wherein:
   (a) the epitope protection positions for the first epitope region are selected from the group consisting of 17 and 89;
   (b) the epitope protection positions for the second epitope region are selected from the group consisting of 52 and 134; and
   (c) the epitope protection positions for the third epitope region are selected from the group consisting of 155 and 265.

7. A protease conjugate according to Claim 6 wherein the epitope protection positions for the first epitope region are selected from the group consisting of 17 and 89.

8. A protease conjugate according to Claim 6 wherein R_2 is nil.

9. A protease conjugate according to Claim 8 wherein R_1 is nil.

10. A protease conjugate according to Claim 8 wherein R_1 is the first polypeptide.

11. A protease conjugate according to Claim 10 wherein the first polypeptide is selected from the group consisting of subtilisin BPN', subtilisin Carlsberg, subtilisin DY, subtilisin 309, proteinase K, thermitase, Protease A, Protease B, Protease C, and Protease D.

12. A protease conjugate according to Claim 11 wherein the first polypeptide is covalently attached to the linking moiety or the protease moiety at a position of the first polypeptide selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 17, 22, 23, 24, 25, 26, 27, 36, 40, 41, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 62, 63, 67, 86, 87, 89, 91, 99, 100, 101, 102, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 140, 141, 143, 144, 145, 146, 154, 155, 156, 157, 172, 173, 187, 189, 195, 197, 203, 204, 206, 209, 210, 212, 213, 214, 215, 216 253, 254, 256, 265, 267, 269, 271, 272, and 275.

13. A protease conjugate according to Claim 12 wherein X is nil and wherein the protease moiety and the first polypeptide are covalently attached through a disulfide bridge.

14. A protease conjugate according to Claim 6 wherein R_1 is the first polymer and R_2 is selected from the group consisting of nil and the second polymer.

15. A protease conjugate according to Claim 14 wherein R_2 is nil and the first polymer is a polyethylene glycol.

16. A protease conjugate according to Claim 15 wherein at least one addition moiety is covalently attached to an epitope protection position for the first epitope region.

17. A protease conjugate according to Claim 15 wherein at least one addition moiety is covalently attached to an epitope protection position for the second epitope region.

18. A protease conjugate according to Claim 15 wherein at least one addition moiety is covalently attached to an epitope protection position for the third epitope region.

19. A protease conjugate according to Claim 1 additionally comprising one or more supplementary moieties selected from the group consisting of small molecules, polypeptides, and polymers.

20. A cleaning composition comprising a protease conjugate according to Claim 1 and a cleaning composition carrier.

21. A personal care composition comprising a protease conjugate according to Claim 1 and a personal care carrier.